If tests for chlamydia are now to be used, which one should be selected? The plethora of tests now available is indeed confusing. For the most part, commercially available laboratory-based tests for chlamydia can be divided into two types—ELISA assays and direct immunofluorescence slide assays. These tests have been reviewed in detail elsewhere.[7] While each type of test has certain advantages and disadvantages, both when properly done achieve acceptable sensitivity and specificity for clinical use. The test that is best performed by the laboratory a physician uses is probably the test to select. For women, a cervical swab is the specimen of choice, and for men, either a urethral swab or a first-void urine specimen can be used. As reviewed by Schachter, attention to specimen collection is critical. Simplified chlamydial diagnostic tests for use in physicians' offices have recently been marketed. Experience with these tests is evolving, but to date they look considerably less sensitive than laboratory-based tests.

A final area of interest for clinicians in Schachter's review is the rapid growth of knowledge regarding *Chlamydia pneumoniae,* the recently discovered third species of the *Chlamydia* genus.[8] This respiratory pathogen appears to be much like *Mycoplasma pneumoniae:* it spreads within families or other closed populations; produces protracted upper and lower respiratory tract illness, including bronchitis and pneumonia; and can be treated with antibiotics. Unfortunately, the diagnosis is not easy to confirm owing to the organism's fastidious growth in cell culture. Noncultural tests are being developed, however, and a more sensitive cell line has recently been described.[9] Infections may occur in epidemic waves in communities, with a large number of infections in some years and few the next. Thus, knowledge of the current local epidemiology of respiratory infection is important. Practically speaking, serologic diagnosis is the only approach currently available to most clinicians. A single chlamydial complement fixation test that is elevated (titer $\geq$1:64) or a fourfold rise or fall in titer that can be demonstrated during acute and convalescent periods provides support for the diagnosis but is not specific—both *Chlamydia psittaci* and *C trachomatis* also cause elevated antibody levels. Currently, the administration of 2 grams of tetracycline or 200 mg of doxycycline is the recommended therapy.

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Neuroleptics and Tardive Dyskinesia—A Case of Iatrogenesis

NEUROLEPTIC-INDUCED TARDIVE DYSKINESIA (TD) is a unique disorder in that it is the only known potentially irreversible movement disorder caused by a therapeutically administered agent. (Irreversible movement disorders can also be induced by drugs of abuse, such as 1-methyl-4-phenyltetrahydropyridine or MPTP, while reversible dyskinesias are caused by levodopa and several other therapeutic agents.) Another paradoxic characteristic of TD is the ability of the causative agents (neuroleptics) to suppress the pathologic movements. Furthermore, the movements of TD do not necessarily worsen with continued neuroleptic use. These findings highlight the complex pharmacologic and toxicologic nature of TD.

Typically, the age of onset of a number of movement disorders is restricted to one particular stage of life; for example, Gilles de la Tourette's syndrome usually develops in childhood or adolescence and Huntington's disease in early or mid-adult life. By contrast, TD can develop in all age groups, with peripheral choreoathetoid movements being somewhat more common in younger patients and elderly patients having predominantly orofacial movements, at least in the early stages.

The article "Tardive Dyskinesia" by Daniel Casey, MD, elsewhere in this issue[1] provides an excellent overview of this clinically important and unusual iatrogenic disorder. As pointed out by Dr Casey, who is a respected major investigator in the field, TD occurs in approximately 20% of patients on long-term neuroleptic treatment, with a greater prevalence found in high-risk groups, such as the elderly and those with mood disorders. Given the efficacy of neuroleptic agents in ameliorating symptoms in debilitating disorders such as schizophrenia, it is of utmost importance that the potentially irreversible side effects of TD and related tardive syndromes be well understood as to their course, prevention, and treatment.

Chronic schizophrenia is the most frequent indication for the prolonged use of neuroleptic medications, with doses often far exceeding those used in patients with other disorders. Yet, there is some suggestive evidence that these patients may be at a lower risk for the development of TD than patients with mood disorders (especially unipolar depression) and nonpsychotic disorders. This leads to questions about possible factors that might be present in persons with schizophrenia that reduce their vulnerability to the development of TD. Is it possible that the patients who seem to need neuroleptic agents the most—that is, schizophrenics—are relatively resistant to the development of a major adverse effect of those medications? If true, the implications of this possibility are fascinating.

In geriatric practice, neuroleptic drugs are commonly prescribed for treating psychosis and agitation in demented patients. Although they are helpful symptomatically, the improvement produced is usually only modest.[2] Medical patients with intractable nausea and vomiting, severe gastroparesis, and other chronic gastrointestinal difficulties are also frequently treated with neuroleptic medications such as prochlorperazine edisylate (Compazine) and metoclopramide hydrochloride (Reglan). In view of the significant risk of TD, it is imperative that the overall risks and benefits of neuroleptic therapy be carefully weighed in this patient population.

The pathophysiologic mechanism responsible for the development of TD is far from clear. Initially, supersensitivity

of the striatal postsynaptic dopamine receptors was thought to be paramount in the development of TD. Although a number of studies in animals have shown an increase in the striatal D2 dopamine-receptor density after the administration of neuroleptics, this finding has not been correlated with the development of TD. The occurrence of such supersensitivity may therefore be thought of as a normal physiologic response to the administration of neuroleptics, rather than as a phenomenon specifically associated with the pathologic process of TD. Furthermore, the postsynaptic dopamine-receptor supersensitivity measured in animals has been shown to decrease rapidly with the termination of neuroleptic treatment, while TD may abate, remain stable, or even progressively worsen in the weeks to months after the cessation of neuroleptic therapy.

It is unlikely that the pathogenesis of TD involves only one neurotransmitter system. There is evidence for the involvement of the noradrenergic, GABA[γ-aminobutyric acid]ergic, cholinergic, serotonergic, and possibly neuropeptidergic systems in the development of TD. The finding that subgroups of TD patients respond to divergent treatment modalities without there being a single globally effective treatment supports the suggestion that TD represents a group of disorders with differing pathophysiologic mechanisms but similar symptomatic presentations.[3] There is, thus, a need to stop thinking of TD as a unitary disorder resulting from dopamine-receptor supersensitivity and, instead, to view TD as a syndrome with several possible neurotransmitter disturbances.

It is conceivable that the development of persistent TD involves neuronal damage at a structural or ultrastructural level. One proposed mechanism for such cellular damage implicates the production of free radicals from the metabolism of catecholamines in the striatum. Some indirect support for the free radical hypothesis of TD comes from a study by Lohr and co-workers wherein an abatement of TD was shown in some patients treated with α-tocopherol or vitamin E, an effective scavenger of free radicals.[4]

As Casey notes, there is no proven safe and effective treatment for TD, although some patients do respond to pharmacologic manipulations, such as discontinuing anticholinergic agents,[5] adding GABAergic agonists or noradrenergic antagonists, or experimental treatments such as vitamin E. Most often patients should be managed using the "less is better" maxim. This can best be achieved by using the lowest effective doses of neuroleptics rather than "drug holidays" in a majority of patients. There is no evidence that drug holidays decrease the risk of the development of TD. Indeed, many patients with psychotic illness may run the risk, while unmedicated, of having an exacerbation of symptoms with personally and socially deleterious sequelae. It is therefore important to elicit the patient's participation in the decision as to whether the risk for the development of TD with continued neuroleptic use outweighs the risk of symptomatic relapse off medication. If the decision to continue neuroleptics is agreed upon, the patient should be maintained on the lowest effective dose. The discontinuation of treatment should be dependent not on arbitrarily predetermined "holidays," but on a patient's ability to maintain asymptomatic functioning without neuroleptic therapy.

There has been a sharp increase in the number of legal actions initiated by patients with TD over the past several years. These cases have generally been based on claims of negligence in the form of inappropriate assessment, failing to properly manage TD, and failing to obtain informed consent.[6] Although there are widely accepted principles on the necessity to obtain and document informed assent or consent, there is much variation from state to state on the particulars of the law. Furthermore, the relevant laws are evolving within each state. Physicians need to keep abreast of the legislative actions and judicial decisions in the state and county in which they practice.

Although neuroleptics can produce potentially irreversible TD, we must also remember that these potent medications have enabled many patients having chronic psychotic disorders to function better than with most other available treatments. Medical science has yet to develop the ideal medication for psychotic and other severe behavioral disorders: one with all the benefits but without any adverse effects. Therapeutic agents that are site-specific to the dysfunctional areas of the brain are still on the research horizon. Recent studies show some promise toward the development of such specific antipsychotic agents, with low rates of extrapyramidal side effects and TD. An example of this type of antipsychotic is clozapine, the use of which is, however, currently limited to treatment-refractory schizophrenic patients because of the relatively high risk of agranulocytosis.[7] The hope of finding effective and safe therapy for severe mental disorders will best be fulfilled with continued basic and clinical research. Until then, careful and judicious use of the available neuroleptic agents, with the consent of patients, is the best approach.

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Modern Technology and Unaffordable Costs

THE FISCAL CRUNCHES that now seem to be occurring in this nation at the national, state, and local levels of our society are disturbing. One wonders why everything seems to cost more with less value received for the dollars and resources spent. This is true in both the public and private sectors of society. Is it possible that the resources needed to support modern technology are already in short supply in relation to